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5.0
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3.2   2.2

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Effect of PGBx on Local Contractile Abnormalities Following
Graded Reduction in Coronary Blood Flow.

by

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In the setting of acute myocardial ischemia, it is increasingly clear that a zone of myocardium exists which although demonstrating decreased contractile ability, maintains potential for contraction. In the present study, PGBx (1 mg i.v.) was administered to dogs following 1 hour of partial coronary occlusion. Within five minutes there was a marked improvement in contractile function in both the subepicardial and subendocardial layers of the ischemic zone. This affect was not seen in a group of control animals.

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These data suggest that PGBx may have a potential role in treatment of acute myocardial ischemia.

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Introduction

Experimental data obtained in our laboratory have shown that coronary occlusion results in an immediate loss of contractile function in the zone subserved by the occluded coronary artery (1, 2). Utilizing strain gauge arches and mercury in silastic length gauges, animal studies have indicated that following abrupt coronary artery ligation, preejection tension in the ischemic zone falls precipitously within the first 15 seconds, continues to fall markedly for up to 5 minutes and then exhibits a gradual decline for several hours (1). Aneurysmal bulging, indicated by both the dramatic decrease in ejection tension to a negative slope in addition to an increase in segment length, occurs within 3 to 12 seconds and is maximal at 15 minutes (1).

More recent studies in our laboratory have evaluated contraction in both superficial and deep layers of the myocardium for 2 hours of total coronary occlusion (3). After restoration of coronary flow, improvement of the contractile abnormality in subepicardial or subendocardial layers was seen. These data indicate that following a total coronary occlusion, permanent damage in contractile function occurred in these zones. These findings are supported by other data from our laboratory indicating that biochemical (sodium:potassium ratios) electron microscopic and electrographic changes consistent with permanent irreversible damage occurred following total coronary occlusion (4).

In man, however, it is clear from angiographic as well as necropsy studies that coronary artery occlusions are usually partial. This has stimulated evaluation of the effect of partial and graded reductions in

coronary flow contraction of the subserved segment. Studies in our laboratory using an animal model which simulates partial coronary occlusion have indicated that a 25% decrease in distal coronary pressure and flow does not result in any significant change in contraction of the supplied area. However, when coronary flow is further reduced to 50% of control, contraction in the ischemic segment decreased to less than 80% with a marked increase in segment length to more than 130% of the control value. Reduction of distal coronary pressure and flow to 75% resulted in a further and more marked decrease in contraction to 55% of control with an increase in segment length to 182% of control value (5). Of interest was the finding that reduction of coronary flow to 100% resulted in no additional changes in either ischemic tension or length.

Studies with PGBx have suggested that it is able to restore oxidative phosphorylation in degenerated mitochondria. Since ischemia results in irreversible dysfunction which, in turn, appears related to destruction of mitochondria it is conceivable that PGBx would be of considerable value in restoring mitochondrial function in this setting and thereby resulting in a return or imporvement of contractile function in the setting of myocardial ischemia. Moreover, if successful, PGBx might prove of considerable value in the setting of sudden death in preventing or restoring not only cardiac but cerebral function which are major limiting features in any eventual improvement in cardiac status.

To evaluate the potential utility of PGBx in favorably modifying the contractile abnormality secondary to partial reduction in coronary flow, local segmental contraction of ischemic myocardium both on a transmural as well as local subendocardial and subepicardial layers was examined in a series

of experiments and compared to a control group.

Methods

Studies were performed in 22 mongrel dogs weighing 25 to 30 kg, anesthetized with intravenous sodium pentabarbitol (30 mg/kg), intubated and ventilated with a Harvard respirator on room air. A left thoracotomy was performed and the heart supported in a pericardial cradle. Standard electrocardiogram lead II was monitored continuously throughout the experiment. Left ventricular pressure was measured either with a Millar catheter tip transducer or with a stiff polyethylene catheter inserted into the left ventricle and attached to a Statham transducer (P23Db). High sensitivity left ventricular end-diastolic pressure and first derivative of left ventricular pressure were obtained with electronic amplifiers and differentiators.

A long segment of the left anterior descending coronary artery was exposed and an electromagnetic flow probe (Micron 1001B) utilized to measure coronary flow. Zero reference was obtained by transiently occluding the vessel.

For assessment of regional function, Walton-Brodie strain gauge arches were placed on the ischemic and nonischemic zones using deep sutures and stretched to 30-40% (1, 2). The ischemic zone was demarcated by recording local electrograms during transient coronary occlusion. For assessment of subendocardial and subepicardial contraction, 2 pairs of 3 megaHz ultrasonic crystals were implanted in a potentially ischemic area, one in the subendocardium and the other in the subepicardial layer in 2 other groups of dogs (3). Endocardial crystals with a diameter of 2.5 mm were inserted

perpendicular to the long axis of the left ventricle through small stab wounds within the inner half of the myocardium. Subepicardial crystals with a diameter of 1.5 mm were inserted diagonally to the surface of the heart in the subepicardium. These subepicardial crystals were placed parallel to the direction of the epicardial fibers at approximately a 90° angle with the line drawn to the short axis of the ventricle. After each experiment, the heart was removed and the position of the crystals corraborated. Recordings were taken on an Electronics for Medicine oscillographic recorder at paper speeds of 50 and 100 mm/sec. At least one hour was allowed for stabilization prior to control recordings.

After obtaining control recordings, a partial coronary occlusion of 50% was performed on the left anterior descending coronary artery with a specially designed adjustable screw clamp. Recordings of lead II of the electrocardiogram, left ventricular pressure, regional tension development and segment length changes from the subepicardial and subendocardial zones, rate of rise of left ventricular pressure and epicardial electrograms were recorded. Recordings were obtained at control, after 1 hour of coronary occlusion, 2 hours of coronary occlusion and after 1 hour of reperfusion. In 8 dogs, partial coronary occlusion was maintained for 2 hours followed by reperfusion. In 8 dogs, a single intravenous bolus of PGBx (1 mg/kg) was administered after 1 hour of partial coronary occlusion, and its effect on the above parameters measured during the subsequent 1 hour of partial coronary occlusion and subsequent reperfusion.

Data Analysis

Values for transmural myocardial tension development were normalized to a control value as 100% (1, 2). Values for end diastolic segment length were normalized to 10 mm (3). Percent shortening was calculated as the difference between end-diastolic and end-systolic length multiplied by 100. Pressure length loops were generated so as to show the instantaneous relationship between left ventricular pressure and segment length. Areas of pressure length loops were calculated by planimetry. Heart rate and blood pressure were calculated and the effect of coronary occlusion and PGBx determined. Results were analyzed statistically using Student's t test for paired and unpaired data wherever appropriate.

Results

Transmural Tension Development

In 6 dogs, coronary blood flow was reduced by 50% of control. Total tension decreased within 5 minutes and stabilized at 69.9 ± 2.3% of control after 1 hour. Administration of PGBx (1 mg/kg i.v.) resulted in an increase in total tension to 75.9 ± 4.8%. After 1 hour, total tension decreased to the level prior to PGBx administration. Reperfusion resulted in a marked improvement to 92.5 ± 7.7% of control.

Segment Length

In a control group of 8 dogs, diastolic segment length, percent change in length (%ΔL) and segment work of the epicardial zone were determined. As seen in Table 1, end-diastolic length increased after 50% coronary flow reduction to 10.3 ± 0.1 mm and remained insignificantly changed throughout the 2 hours of coronary occlusion. Percent ΔL decreased markedly following

coronary occlusion from $7.3 \pm 0.8\%$ to $1.8 \pm .3\%$ and demonstrated no improvement throughout the period of coronary occlusion (Fig. 1). Similarly, segment work decreased to $28 \pm 6\%$ and remained unchanged. The endocardial zone showed similar directional changes in end diastolic length. However, $\%\Delta L$ and the pressure length loop were more markedly affected by coronary flow reduction (Fig 1).

In a second group of 8 dogs, similar changes in end-diastolic length, $\%\Delta L$ shortening and pressure length loops were seen after partial coronary occlusion (Table 1, Fig. 1). PGBx administered 1 hour after partial coronary occlusion resulted in a significant increase in $\%\Delta L$ both in the epicardial and endocardial layer (Fig. 2). Epicardial systolic shortening increased from 1.1 ± 0.4 to $2.4 \pm 0.5\%$ ($p < .01$) while endocardial $\%\Delta L$ improved from -1.1 ± 0.3 to 0.9 ± 0.4 ($p < .01$) (Fig. 1). Similarly, segment work (PLL area) also increased in the epicardium from 26% to 48% $p < .05$ and in the endocardium from -17% to 28% ($p < .05$) (Fig. 3). One hour after administration of PGBx, both $\%\Delta L$ and segment work had returned to the pre-PGBx level in both the epi and endocardial layers (Fig. 1, 3).

Reperfusion

Following coronary reperfusion, tension development, end-diastolic length, percent systolic shortening and pressure length loops were found to return to normal in both groups of animals.

Blood Pressure and Heart Rate

As seen in Table 1, no significant changes in systolic pressure or heart rate were seen either after partial coronary occlusion, PGBx administration or reperfusion.

Discussion

Early studies with PGBx indicated that it is able to restore oxidative phosphorylation in degenerated mitochondria. Since ischemia results in irreversible dysfunction and appears related to destruction of mitochondria, it is conceivable that PGBx would be of considerable value in restoring mito-chondrial function in this setting and thereby result in return or improvement of contractile function. In vivo studies by Drs. Polis and Angelakos have indicated that PGBx had dramatic effects on myocardial infarction in monkeys. Recovery from fibrillation after acute coronary ligation (defined as main-tenance of effective blood pressure without support) was obtained after 4 minutes of fibrillation in 60% of controls and 100% of PGBx treated animals ($p < .02$). After 12 minutes of fibrillation, cumulative survival was 20% of controls and 88% in the PGBx treated group ($p < .001$). Thus, these studies strongly suggested that PGBx would be of value in decreasing ischemia and improving contractile function in the setting of myocardial ischemia.

The present study indicates that PGBx exerts a beneficial effect on the zone of myocardial ischemia. In the control group, a 50% coronary occlusion resulted in a reduction in tension development and deterioration in segment shortening without any significant improvement throughout the period of occlusion. In contrast, in the group of animals in whom PGBx was administered, significant improvement in both local tension and segment shortening occurred. This improvement was seen in both subendocardial and subepicardial regions. In addition, data obtained from pressure length loops, which are a sensitive measure of local contractile ability of the ischemic portion of left ven-tricle, further supported these data.

Implications

These data support the view that PGBx has beneficial effects on abnormal contraction which occurs following a reduction in coronary blood flow. It is conceivable that this improvement, if found to persist with repeated injections, might result in preservation of ischemic myocardium in the absence of reperfusion. Such preservation is currently receiving increasing attention due to the absence of any safe approach to acutely improve coronary blood flow (6). These data suggest that further work with PGBx is warranted in order to determine its role in preserving ischemic myocardium.

TABLE 1

EFFECT OF PARTIAL CORONARY OCCLUSION, PGBx AND REPERFUSION ON SEGMENTAL FUNCTION

		Control	1 hr	5 min PGBx	2 hr	1 hr RP
PGBx Group						
Epi	EDL	10	10.4 ± .1	10.4 ± .1	10.4 ± .1	10.3 ± .2
	%ΔL	9.3 ± .7	1.1 ± .4	2.4 ± .5	1.3 ± .3	8.3 ± .6
Endo	EDL	10	10.6 ± .1	10.5 ± .1	10.5 ± .1	10.4 ± .2
	%ΔL	14.8 ± .5	-1.1 ± .3	0.9 ± .4	-0.8 ± .4	14.1 ± .7
Control Group						
Epi	EDL	10	10.3 ± .1	-	10.2 ± .1	10.2 ± .2
	%ΔL	7.3 ± .8	1.8 ± .3	-	2.2 ± .4	7.0 ± .5
Endo	EDL	10	10.3 ± .1	-	10.3 ± .1	10.2 ± .2
	%ΔL	13.4 ± .6.	-0.9 ± .4	-	-0.8 ± .3	12.0 ± .6
PGBx						
Syst pressure (mmHg)		140 ± 7	136 ± 7	134 ± 7	136 ± 8	135 ± 8
Heart Rate		133 ± 6	136 ± 6	138 ± 5	139 ± 6	136 ± 8

FIGURE LEGEND

Fig. 1: Effect of partial coronary occlusion for 2 hours, PGBx and reper-
fusion of one hour on percent systolic shortening (%ΔL). Arrow
represent 5 minutes after intravenous infusion of PGBx.

Fig. 2: Control tracing reveals normal endocardial (Endo) and epicardial
(Epi) systolic shortening. Following partial coronary occlusion,
there is a decrease in systolic shortening most marked in the sub-
endocardial layer which improves after administration of PGBx.
Both zones return to normal after reperfusion (see text).

Fig. 3: Simultaneous pressure length loops demonstrate a marked decrease
in loop area with appearance of a figure of 8 in the subendocar-
dial region following coronary occlusion. PGBx results in marked
improvement in both zones indicating improved systolic work.

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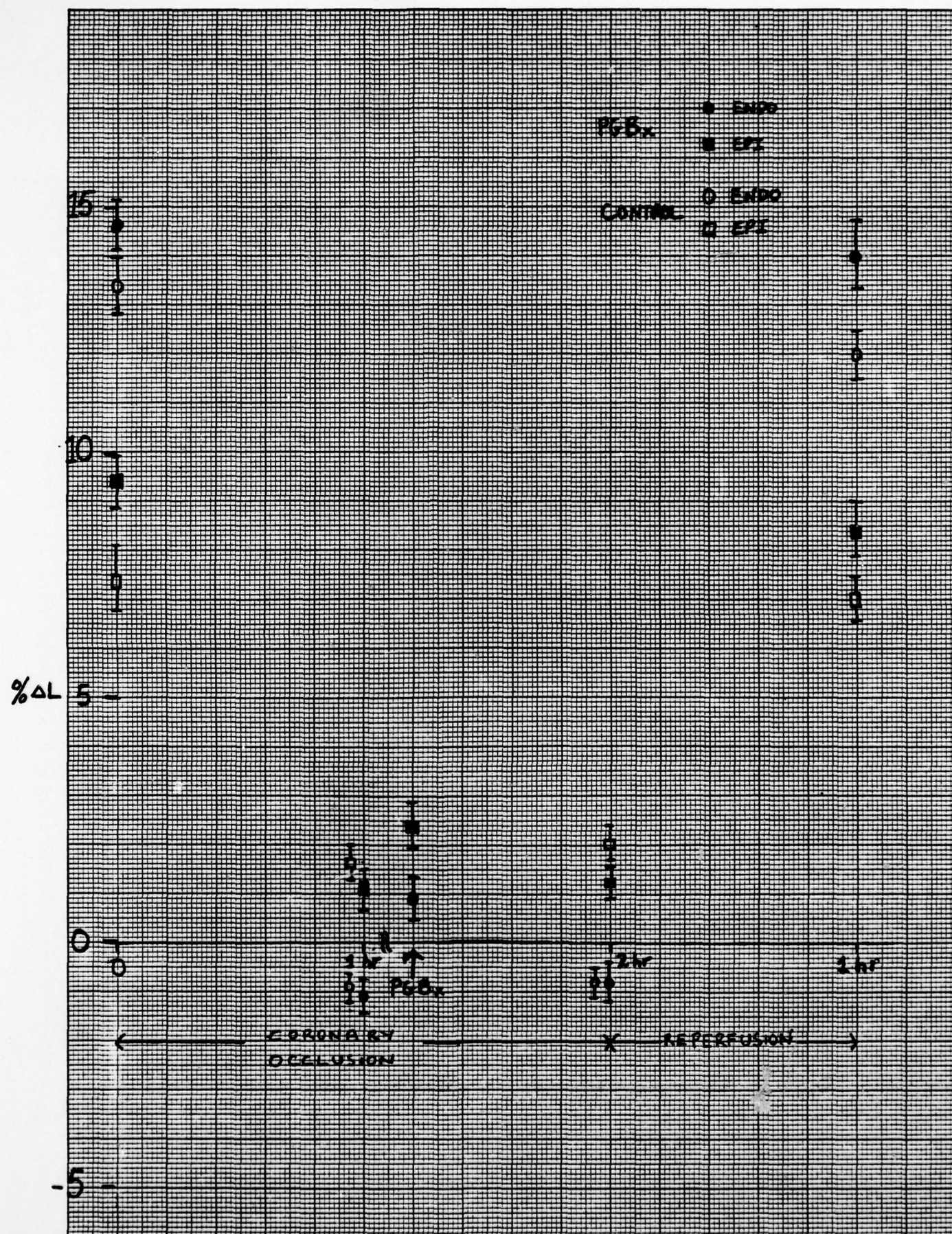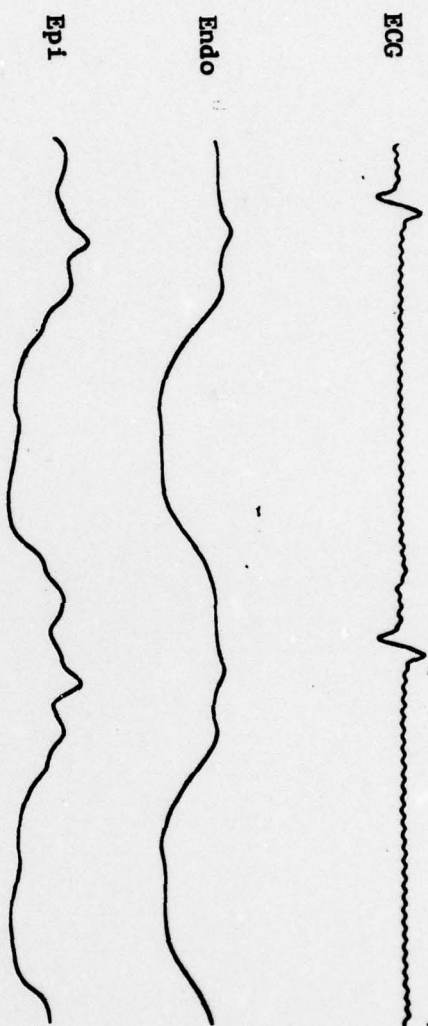   41:345, 1978.
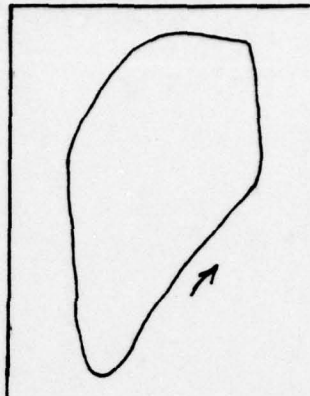
Figure 1

Figure 1

Control

Figure 1

Pre PGBx

Epi

Endo

ECG

Figure 1

Post PGBx
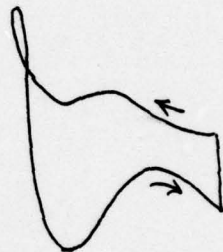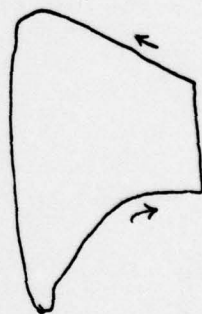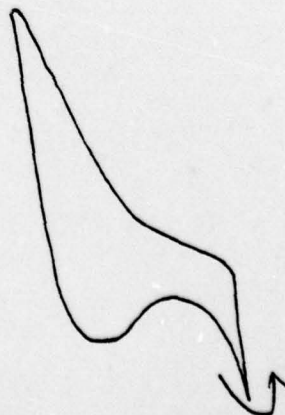
Figure 1

After Perfusion

ECG

Endo

Epl

Epi

P

P

Endo

L

L

CONTROL

AFTER PO
pre PGBx

5 min after PGBx

Reperfusion